IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Judith Fitzpatrick, Regina B. Lenda and Christopher L. Jones

Serial No.: 09/526,582 Art Unit: 1641

Filed: March 16, 2000 Examiner: Gary W. Counts

For: *METHOD AND DEVICE FOR DETECTION OF APO A, APO B AND THE RATIO THEREOF IN SALIVA*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-22 in the Office Action mailed June 2, 2003, in the above-identified patent application. A Notice of Appeal was mailed on September 2, 2003. A check in the amount of $220.00 for the filing of this Appeal Brief with a one month extension of time for a small entity is also enclosed.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Serex, Inc, which has been purchased by Nymox Pharmaceutical Corporation, Saint-Laurent, Quebec, Canada.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-22 are pending. Claim 23 has been cancelled. Claims 1-22 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the amendment mailed on September 2, 2003. In the advisory Action mailed on October 1, 2003 the Examiner indicated the amendment would be ENTERED.

(5) SUMMARY OF THE INVENTION

The claims are directed to a method to determine the level of an apolipoprotein in an individual's serum based on the levels of the apolipoprotein in the individual's saliva (page 6, lines 23-26). The claimed method entails obtaining a saliva sample from an individual and reacting the saliva sample with antibodies that are immunoreactive with apolipoproteins to measure the antibody-apolipoprotein complexes in a quantitative assay (page 19, lines 23-24; page 13, lines 18-25). The method also entails determining the amount of lipoprotein in the individuals serum by comparing the immunoreactivity of the apolipoproteins in the saliva sample and correlating it with the standards of known amounts of apolipoproteins in the saliva and serum (page 19, lines 20-22). The apolipoprotein can be Apo A, Apo B, Apo C, and Apo E

(pages 8-10) but is preferably Apo A1 and Apo B (page 8, line 5; page 12, line 17). The amount of albumin can be detected in the saliva sample (page 20, line 27) and the albumin level can be used to correct the determined about of the apolipoprotein in the saliva sample (page 20 lines 27-31). The antibodies can be labeled with a detectable label (page 12-page 13). The apolipoprotein level can be detected within 3 hours of collection (page 10, line 20). The saliva sample can be prepared prior to determining the apolipoprotein level by removing mucopolysaccharides (page 10, line 18). The saliva can be stimulated from the individual (page 7, lines 8-10). The saliva sample can be collected into a device that filters out mucopolysaccharides and contains antibodies immunoreactive with apolipoproteins (page 11, lines 1-19).

An assay device or kit for use with this method is also claimed. The assay device or kit has a means for collection of saliva, and antibodies to apolipoproteins for use in a quatitative assay to determine levels of apolipoprotein in serum and saliva (pages 10-12; page 18, lines 20-22). The assay device or kit can have a means to remove mucopolysaccharides from the saliva (page 10, line 18), antibodies to apolipoproteins and albumin (page 8-10; page 20, line 1) and reagents to detect apolipoprotein-antibody complexes (page 12, lines 10-22). The antibodies can be immobilized on a solid support or dipstick (page 14-15).

This method can also be used to quantitate the amount of lipoprotein or cholesterol in saliva, lipid disorders or risk of cardiovascular disease from a saliva sample (page 6, line 30, page 14, lines 11-15). The saliva sample can be reacted with antibodies immunoreactive to apolipoproteins to determine the amount of antibody-apolipoprotein complexes (page 18, lines

18-29) and correlating with standards of known amounts of apolipoproteins in saliva and serum from normal and at risk individuals (page 18, line 20-22; page 6, lines 27-30).

The levels of low density lipoprotein and high density lipoprotein in serum can also be determined with this method by correlating the levels of apolipoprotein subtypes in the serum based on apolipoprotein levels in saliva and then extrapolating the serum apolipoprotein levels based on the saliva apolipoprotein levels (Figures 1, 2, and 3a; page 9, lines 13-17 and page 9, line 23-24).

(6) ISSUES ON APPEAL

The issues presented on appeal are:

(1) whether claim 19 is clear and definite as required by 35 U.S.C. § 112, second paragraph;

(2) whether claims 1-3, 5-7, 10-14, 16-18 and 20-22 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 ("Oberhardt '991") in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and further in view of U.S. Patent No. 6,291,178 to Schneider ("Schneider")

(3) whether claims 1-4 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 6,210,906 to Kundu et al. ("Kundu") in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and further in view of U.S. Patent No. 6,291,178 to Schneider ("Schneider")

(4) whether claims 8-9, 15 and 19 are obvious under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 to Oberhardt ("Oberhardt '991") in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman")

and further in view of U.S. Patent No. 6,291,178 to Schneider ("Schneider") and in further view of Fisher et al. (Diabetes Research and Clinical Practice, 1991) ("Fisher") and Coppo et al. (Journal of Diabetic Complications, 1987) ("Coppo").

(7) GROUPING OF CLAIMS

The claims do not stand or fall together. The claims can be grouped as follows: (1) claims 1-11, (2) claims 12-19 and (3) claims 20- 22. Claims 1-11 define a method of detecting apolipoprotein in a saliva sample and correlating it to a blood sample. Claims 12-19 are directed to an assay device or kit having antibodies to apolipoprotein and a collection device for saliva for detecting the amount of apolipoprotein in a saliva sample. Claims 20-22 are directed to a method of detecting the amount of lipoprotein or HDL/LDL in a saliva sample to monitor an individual's risk of CAD.

(8) ARGUMENTS

(a) The Claimed Invention

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in most developed countries. Numerous markers and test for identifying individuals at risk are available, among them blood tests for lipid markers such as total cholesterol and cholesterol bound to various circulating proteins. Based on the outcome of such testing, appropriate prophylactic or therapeutic measures including dietary modification and exercise can be initiated to forestall or reverse progression to more severe CAD.

A large number of manual and automated methods are available for screening and monitoring of these markers. All of these tests, however require either venous blood drawn by

syringe or in some cases capillary blood obtained by needle prick. Both methods are invasive and unpleasant to many individuals and are best performed by trained professional personnel in a doctor's office to minimize erroneous results. Handling and disposal of blood products also involves potential hazards from infectious agents and pathogens.

Most analytes that appear in serum also appear in saliva at a fraction of the level seen in serum. Saliva has not been exploited as a diagnostic fluid because of the many problems associated with adapting it to assay form. Most tests require large volumes of saliva (at least 1mL) because so much is lost during handling and preparation. Saliva has to be filtered to remove mucopolysaccharides and stored with preservatives for shipment to a laboratory. Sufficient quantities of saliva can be acquired when flow is stimulated (for example by a breath mint) but stimulated samples have different levels of analyte than samples taken with normal saliva flow and creates variability between samples and prevents accurate analyte detection.

Although it was postulated that apolipoproteins were present in saliva, it was not previously known that the levels could be correlated to serum levels, thereby making a non-invasive test using saliva a possibility. It was not clear from the early literature whether the salivary lipids are synthesized *de novo* in the salivary glands or were derived from serum. If they were serum derived, it was not known if the salivary apolipoproteins are the same as the apolipoproteins that are associated with LDL and HDL in serum. Furthermore, analyte concentration in stimulated saliva samples is substantially diluted making quantification impossible. These problems are compounded with the fact that many analytes are degraded by salivary enzymes.

The Appellants have developed a method to detect the levels of an analyte, such as apolipoproteins A-1 and B, in saliva which can be correlated with the levels of HDL and LDL in serum. The ratio of ApoA to Apo B is correlated with the ratio of HDL to LDL in serum. The advantages of such a system are readily apparent: one does not have to draw a blood sample, process it to remove the red cells, and subsequently assay it to determine the apolipoprotein levels.

In stimulated saliva, the levels of ApoB are normalized to albumin and correlate with both serum Apo B and serum LDL. Normalizing the saliva sample to albumin overcomes the analyte variability in stimulated samples. The combination of a high degree of correlation with a simple quick test that can be performed a the site of collection provides a cost effective, patient friendly means to monitor an individual's risk of heart disease. The assay of saliva at the point of collection eliminates the need for preservatives to store the sample and entirely avoids problems associated with contamination by oral flora and sample degradation en route to a laboratory.

The Examiner's position is that such a saliva-serum correlation of apolipoproteins is obvious. It is not. In fact, the dogma at the time of filing was that there was so much inherent variability in the saliva that although apolipoprotein was clearly present, the samples could not routinely be assayed and yield a reliable result. The claimed method provides a non-invasive method to determine the serum levels of HDL and LDL as a diagnostic assay for the risk of CAD.

(b) Rejections Under 35 U.S.C. § 112

i. Rejection of Claim 19 under 35 U.S.C. § 112, second paragraph

Claim 19 was rejected as indefinite for failing to identify how claim 19 differs from claim 17.

The amendment to claim 19 filed on October 1, 2003 and entered by the Examiner more clearly defines the antibodies to the apolipoproteins as a first reagent (in a first reagent container) and the antibodies to the albumin as a second reagent (in a second reagent container), not as a single mixed antibody solution. Antibodies to albumin are used to correlate the concentration of proteins in the saliva and serum as described on pages 19-20 of the specification.

Claim 19 is different than claim 17. Claim 17 further defines the kit of claim 16 by defining reagents for the detection of antibody-apolipoprotein complexes. These reagents are described on page 12-13 of the specification and include for example secondary antibodies labeled with fluorescent and enzymatic markers. The anti-albumin antibodies of claim 19 bind to albumin, not antibody-apolipoprotein complexes.

(c) Rejections Under 35 U.S.C. § 103

i. Rejection of Claims 1-3, 5-7, 10-14, 16-18 and 20-22 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 ("Oberhardt '991") in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and further in view of U.S. Patent No. 6,291,178 to Schneider ("Schneider")

The Legal Standard

The law is quite clear that to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. These two factors must be founded in the prior art, not the Appellant's disclosure. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. "Teaching away" is a further indicia of non-obviousness which is properly considered in regards to an obviousness rejection, *In re Hedges*, 228 USPQ at 687.

Particularly relevant to this rejection are the decisions of the Court of Appeals for the Federal Circuit in *In re Dow Chemical*, 5 USPQ2d 1529 (1988) and *In re Vaeck*, 20 USPQ2d 1438 (1991). The *Dow* Court notes that:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art... Both the suggestion and

> expectation of success must be founded in the prior art, not in the applicant's disclosure.

Furthermore,

> In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered: for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention...Evidence that supports, rather than negates, patentability must be fairly considered.

5 USPQ 2d at 1531-1532 (Citations omitted).

Similarly, in *In re Vaeck*, the Federal Circuit stated:

> Where claimed subject matter has been rejected as obvious in view of a combination of pprior art references, a proper analysis under §103 required, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process: and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed.Cir. 1988).

20 USPQ2d at 1442.

The Prior Art

The prior art does not disclose each claimed element. In particular, the prior art fails to disclose at least one critical element - that *saliva apolipoprotein levels* can be correlated with *serum apolipoprotein levels.*

Oberhardt '133 and '991

The Examiner has relied on Oberhardt for the teaching of detecting apolipoproteins in saliva with antibodies. Oberhardt '991 discloses a method and a system of dry chemistry cascade immunoassay and affinity assay. Neither Oberhardt patent discloses the correlation between apolipoprotein levels in saliva and blood. Neither of these patents enables one of ordinary skill to detect the levels of lipoproteins in saliva and extrapolate to the serum concentrations.

Fellman

The examiner has relied upon Fellman for showing that saliva can be collected.

Fellman discloses a means for reducing the viscosity of a body fluid sample such as saliva which contains mucopolysaccharides, using a cationic quaternary ammonium reagent. Fellman does not disclose detecting apolipoproteins in saliva with antibodies, or that the levels can be correlated with levels in serum. Fellman does not disclose a quantitative assay kit comprising collection mean, antibodies to apolipoprotein, and means to compare saliva and serum apolipoprotein levels.

Schneider

The Examiner has relied on Schneider for the teaching that it is known in the art to correlate a saliva sample with a blood sample to determine an amount of analyte of interest.

The patent application that issued as U.S. Patent No. 6,291,178 ("Schneider") was filed on August 30, 1999 as a CIP of U.S.S.N. 08/978,729, now U.S. Patent No. 5,968,746. A review of the '746 patent clearly demonstrates that it does not disclose that apolipoproteins can be measured in saliva, and their concentrations correlated. The priority date of the present application is March 16, 1999 and therefore the '178 patent is unavailable as prior art to the present application. The Examiner asserts that the prior '746 patent discloses that analytes are present in saliva whose concentrations can be correlated to serum levels. This is not the same, however, as showing that apolipoproteins fall into this category of analytes. No prior art has been cited that says that the concentrations of apolipoproteins in saliva can be correlated with the concentrations of apolipoproteins in serum.

There are several other aspects of Schneider that are different from the claimed technology. First, Schneinder is a qualitative not a quantitative assay. This is a major difference. It is also why Schneider's system provides for extensive dilution of sample -which may alter the amount of apolipoprotein measured in a given volume, thereby completely destroying the ability to correlate the levels of apolipoprotein measured in the sample with the levels measured in the serum. Second, Schneider's system is primarily drawn to measurements of other molecules, such as ethanol, which are known to have a correlation between saliva levels and serum levels, unlike in the present case. It is interesting to note that the later filed application corresponding to

the '178 patent is directed to a method for detecting cholesterol from saliva. This aspect of their method was conspicuously absent in the parent application. The parent application was directed to a method to detect alcohol in saliva. This would indicate that one of skill in the art was not aware that this method could be used to detect apolipoproteins and cholesterol prior to the filing date of the present application.

Schneider discloses that the levels of blood alcohol can be correlated between saliva and serum. It is known in the art that analytes can be found in both serum and saliva. This concept is disclosed on page 3, lines 3-8 of the present specification. The novel feature of this work is that a *quantitative* assessment of the serum *apolipoprotein* concentration can be correlated with saliva *apolipoprotein* concentration.

Claims 1-3, 5-7, 10 and 11 are not obvious in view of Oberhardt, Fellman or Schneider

As described above, Oberhardt is deficient in detecting apolipoprotein levels, correlating the levels of apolipoprotein in blood and saliva as well as collecting and preparing a saliva sample for assay. Fellman discloses a method to remove mucopolysaccharides in a saliva sample for detection of an analyte. Fellman does not disclose detection of apolipoprotein or the quantitiative correlation of apolipoprotein levels between saliva and serum. Schneider does not make up for these deficiencies.

As previously mentioned, Schneider is a qualitative, not a quantitative, assay to detect hydrophilic compounds. This is a major difference. It is also why Schneider's system provides for extensive dilution of sample – which may alter the amount of apolipoprotein measured in a given volume, thereby completely destroying one's ability to correlate the levels of

apolipoprotein measured in the sample with the levels measured in the serum. Second, Schneider's system is primarily drawn to measurements of other molecules, such as ethanol, which are known to have a correlation between saliva levels and serum levels, unlike in the present case. It was not previously known whether the salivary apolipoprotein levels were synthesized *de novo* in the salivary gland or derived from serum (paragraph bridging pages 5 and 6 of the specification).

Schneider discloses that hydrophilic compounds can be detected in saliva and mentions hydrophilic proteins (column 2, line 41). Apolipoprotein is not a hydrophilic protein. It is amphipathic. The carboxy terminal part of the protein is hydrophobic. The mixed nature of apolipoprotein accounts for the ability of apolipoprotein to bind lipids. The disclosure of Schneider clearly states that their method is not appropriate for non-hydrophilic proteins (column 2, lines 31-54). One would not be motivated to use the method of Schneider to examine proteins with hydrophobic properties because one would not expect them to be fully soluble in the aqueous solution to obtain an accurate reading.

In *In re Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* (00-1467 Fed. Cir. 2003), the Court state that "to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc,*. 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every

element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.")

The disclosure of Schneider does not enable one of skill in the art to correlate the salivary apolipoprotein levels to serum apolipoprotein levels. Schneider does not disclose proper handling of a saliva sample to preserve the apolipoprotein from degradation. In fact Schneider discloses those exact conditions (i.e. the presence of proteolytic salivary enzymes) that the Appellants have demonstrated cause degradation of the salivary apolipoprotein target. Schneider also discloses the problems of maintaining a serum sample specifically to prevent degradation of the alcohol content. Schneider does not disclose methods to prevent degradation of apolipoproteins by salivary enzymes. In fact, Schneider discloses that salivary proteases exist in saliva that degrade salivary proteins (column 3, line 11-16). The present specification teaches that apolipoprotein degradation occurs in saliva within one hour at room temperature (page 17, lines 15-31). One of skill in the art would not be motivated to apply the disclosure of Schneider to the present method with any expectation of success.

Schneider specifically discloses a method that entails collecting a sample and then sealing and transporting to an off-site laboratory for later testing (column 6, lines 46-51). This is in direct conflict with the present method which teaches assay at the point of collection or immediately thereafter to prevent putrefication of the sample and degradation of the proteins. "A prima facie case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)

It is significant that Schneider did not include apolipoproteins in the '178 patent specification and added reference to cholesterol and apolipoprotein in the subsequent continuation-in-part (CIP) application filed August 30, 1999. This is because it was not known prior to filing the CIP that apolipoprotein could be correlated between saliva and serum. This element is not taught in any of the cited references. One of skill in the art would not be motivated to use the disclosure of Schneider to detect apolipoprotein in saliva absent the teachings and examples of the present specification.

Schneider also discloses that excretion of protein by parenchymal cells into the saliva is hindered by the presence of enzymes that degrade the proteins into peptides and amino acids (col 2, line 62 to col 3,line 16). The presence of aminopeptidases and hydrolysis of peptides in saliva is well known in the art. In a *quantitative* assay such as the one claimed, degradation of the target is a serious problem. It would be highly problematic to obtain a quantitative reading of proteins and correlation to serum concentrations of a protein that was easily degraded. Applicants teach preservation of the saliva sample on page 10, lines 18-22 by refrigerating the sample, adding protease inhibiting enzymes and testing the sample for the analyte within 3 hours of collection before major degradation can occur. One of skill in the art would not have expected a correlation between serum and saliva apolipoprotein levels using the method of Schneider because of the degradation of salivary proteins. The method of Schneider is effective for detecting the presence of drugs (such as ethanol) that are not degraded by proteolytic enzymes or even detecting the presence of proteins in saliva. Based on the teachings of Schneider, one of skill would realize that the improper sample preservation in the method of Schneider would

render a correlation totally impossible. Schneider does not disclose that saliva apolipoprotein levels can be correlated with serum apolipoprotein levels. Schneider provides no teaching or example that apolipoproteins can be detected using their method and discloses that it is likely not possible.

Conversely, Appellants have demonstrated that despite the negative teachings of Schneider, it is possible to read the concentration of apolipoprotein in a saliva sample and correlate it to serum apolipoprotein levels. Despite the negative teachings of Schneider, the Appellants have shown that degradation of the salivary apolipoprotein can be controlled and quantitative data can be obtained which can be correlated to serum apolipoprotein levels. These results are unexpected in view of the knowledge in the art and the disclosure of Schneider.

In view of the above discussion, Oberhardt in combination with Fellman and Schneider neither discloses or makes obvious the claimed method. One of skill in the art would not be motivated to combine these references to obtain a quantitative assay of serum apolipoprotein in view of the lack of guidance in the art and the negative teachings of Schneider.

Claims 12-14 and 16-18 are not obvious in view of Oberhardt, Fellman or Schneider

Claims 12-14 and 16-18 are directed to an assay device or kit to detect apolipoprotein in saliva and correlate it to serum apolipoprotein levels. As described above, this combination of prior art references fails to disclose a method to detect apolipoprotein in saliva and correlate it to serum apolipoprotein levels. As such, as assay device or kit directed to this methods is not obvious in view of the cited art.

Claims 20- 22 are not obvious in view of Oberhardt, Fellman or Schneider

Claims 20-22 are directed to a method of detecting lipoprotein or cholesterol. Schneider does not disclose a correlation between serum and saliva LDL/HDL cholesterol concentrations until after the filing date of this application. As this claim element is not disclosed by the cited art, the claimed method is not obvious in view of this combination of references. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)

ii. Rejection of Claims 1-4 under 35 U.S.C. § 103(a) over over U.S. Patent No. 6,210,906 to Kundu et al. ("Kundu") in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and further in view of U.S. Patent No. 6,291,178 to Schneider ("Schneider")

The Prior Art

Kundu

The examiner has relied upon Kundu for the detection of apolipoprotein A in a saliva sample by reacting monoclonal antibodies with the apoliprotein (column 4, lines 39-52 and column 8, lines 8-15). Certainly column 4 refers to reaction of an antibody with a protein in a sample containing an apolipoprotein, but there *is no mention of saliva.* Column 8 does refer to samples as including saliva.

Kundu discloses specific antibodies to Apo A and methods to use the antibodies. Similar to the Oberhardt patents, Kundu does not disclose why or how the levels of apolipoproteins should be detected in saliva, nor how to correlate the levels of the apolipoproteins in the saliva

with the levels of the apolipoproteins in the serum, as defined by the claims. Kundu does not disclose removal of mucopolysaccharides, or reasons to remove mucopolysaccharides.

Claims 1-4 are not obvious in view of Kundu, Fellman and Schneider

Kundu does not disclose a quantitative assay to detect Apo A in saliva and correlate it to serum Apo A concentrations. Fellman discloses a method to remove mucopolysaccharides from saliva to prepare a saliva sample for assay but does not suggest detecting apolipoproteins or correlating those values with serum levels. As discussed above, Schneider does not provide the necessary guidance to make up for these deficiencies. One of skill in the art would not be motivated to combine these references absent the teachings of the present specification with any expectation of success.

The teachings and examples of the present specification make up for the deficiencies of Kundu, Fellman and Schneider by teaching that a *quantitative* correlation can be determined between apolipoprotein levels in saliva and blood and that the saliva sample can be properly treated immediately after collection to prevent degradation of salivary proteins. These elements are not disclosed in part or in total by the cited references.

It has been made very clear that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Further, the "level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-site Corp v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

There is no motivation in the cited art that would suggest combining these references and then modifying them for a different purpose, as Appellants have done. There is no motivation to combine these references and obtain all the claim elements. Kundu does not recite a need to remove mucopolysaccharides from the sample and Fellman does not recite a need to use their method to detect apolipoprotein levels.

iii. Rejection of Claims 8-9, 15 and 19 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,677,133 to Oberhardt ("Oberhardt '133") or U.S. Patent No. 5,601,991 to Oberhardt ("Oberhardt '991") in view of U.S. Patent No. 5,112,758 to Fellman et al. ("Fellman") and further in view of U.S. Patent No. 6,291,178 to Schneider ("Schneider") and in further view of Fisher et al. (Diabetes Research and Clinical Practice, 1991) ("Fisher") and Coppo et al. (Journal of Diabetic Complications, 1987) ("Coppo").

The Prior Art

Fisher and Coppo

The examiner has relied on Fisher and Coppo for "normalizing the amount of apolipoprotein to the amount of albumin present in the saliva sample and antibodies immunoreactive to albumin in the device or kit for determining apolipoprotein concentration."

Fisher and Coppo provide assays for detecting albumin, one in saliva and one in urine. Neither suggest detecting apolipoprotein in saliva, nor that the levels could be correlated with the levels in the serum by measuring the values of the albumin.

Claims 8-9 are not obvious in view of Oberhardt, Fellman, Schneider, Fisher and Coppo

As described above, the claimed method is not disclosed in whole or inpart by the cited references and the cited references are deficient in any suggestion to combine to arrive at the claimed method. Kundu does not teach a means for collecting saliva nor a process to correlate the results of saliva and serum. Fellman does not recite a need to use their method to detect apolipoprotein levels. There is no motivation to combine these references and modify them as Appellants have done. Fisher and Coppo do not make up for these deficiencies. One of skill in the art would not find the claimed methods or kit obvious absent the teachings of the present specification.

At the time of this application was filed, there was so much inherent variability in the saliva that although apolipoprotein was clearly present, the samples could not routinely be assayed and yield a reliable result. The examiner's attention is drawn to the prior art discussed at page 4 of the application in this regard. The examiner has provided no art that demonstrates that the prior art was not entirely inconsistent.

Claims 15 and 19 are not obvious in view of Oberhardt, Fellman, Schneider, Fisher and Coppo

As discussed above, Oberhardt, Fellman and Schneider in combination do not render the claimed method obvious. Claims 15 and 19 define an assay device or kit directed to this method that normalizes the levels of apolipoprotein detected in saliva to known standards of albumin to correlate saliva and serum concentrations. Fisher and Coppo provide assays for detection of albumin in saliva and urine. Neither suggest detecting apolipoprotein in saliva or correlating with serum levels for quantitative assay of apolipoprotein levels. Fisher and Coppo fail to

address the deficiencies of Oberhardt, Fellman and Schneider and do not provide sufficient motivation to use albumin standards to obtain quantitative results correlating the levels of apolipoprotein between saliva and blood.

(9) SUMMARY AND CONCLUSION

The Appellants have developed a novel and unobvious non-invasive assay for detecting serum apolipoprotein levels. The cited references do not disclose all claim elements nor do they provide the necessary motivation and teaching to warrant combination to arrive at the claimed method to detect apolipoprotein. The following statements of the Examiner, assert the contribution of each reference:

"The examiner has cited Oberhardt '991 and '133 for the purpose of showing that one can monitor magnetic particle response to determine the concentration of apolipoprotein in a sample, which may be saliva."

"The examiner has relied upon Fellman for showing that saliva can be collected."

"The examiner has relied upon Kundu for the detection of apolipoprotein A in a sample that can be saliva by reacting monoclonal antibodies with the apoliprotein (col. 4, lines 39-52 and col. 8, lines 8-15)."

Schneider '178 is cited by the examiner as "teaching that it is known in the art to correlate a saliva sample with a blood sample to determine an amount of analyte of interest."

The examiner has relied on Fisher and Coppo for "normalizing the amount of apolipoprotein to the amount of albumin present in the saliva sample and antibodies immunoreactive to albumin in the device or kit for determining apolipoprotein concentration."

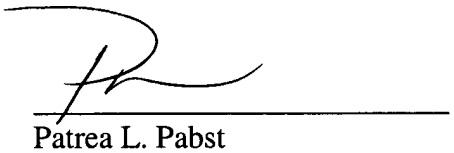
Conspicuously absent, the examiner has failed to cite any prior art that teaches that one could determine levels of apolipoprotein in saliva and correlate these levels to the levels of apolipoprotein in serum. The only way the examiner can reach this conclusion is from Appellants' specification – and hindsight reconstruction is not permitted. 35 U.S.C. 103 requires that the claimed subject matter must be obvious from the cited art – i.e., that the elements are disclosed and one skilled in the art is provided with the motivation to combine as Appellants have done, with a reasonable expectation of success. There is no ***prior art*** that would lead one skilled in the art to this conclusion. Indeed, the prior art Schneider actually ***teaches away*** from such a conclusion.

The Examiner has selectively relied upon a myriad of references to assemble an approximation of the claimed method and assay device/kit. The Examiner has consistently avoided disclosure in all references that teach away from the claimed method and has assembled a similar assay in view of the teachings of the specification. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984).

The combination of cited references does not provide a suggestion to combine or a reasonable expectation of success without the teachings of the present specification. The legal standard has been met.

For the foregoing reasons, Appellant submits that the claims 1-22 are patentable.

Respectfully submitted,



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Date: December 2, 2003

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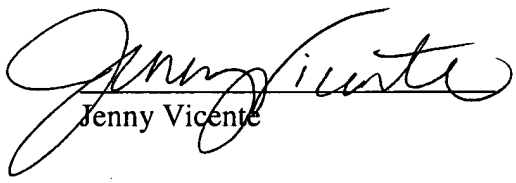

Jenny Vicente

Date: December 2, 2003

Appendix: Claims On Appeal

1. (previously Three times amended) A method for determining the level of an apolipoprotein in the serum of an individual based on levels of the apolipoprotein in the individual's saliva comprising

obtaining a saliva sample from an individual,

reacting the apolipoproteins in the saliva sample with antibodies immunoreactive with one or more of the apolipoproteins, wherein the antibodies are in a quantitative assay which measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith,

determining the amount of apolipoproteins in the serum of the individual by comparing the immunoreactivity between the antibodies and apolipoproteins in the saliva sample by reference to standards of known amounts of apolipoproteins in saliva and serum.

2. (previously once Amended) The method of claim 1 wherein the apolipoprotein is selected from the group consisting of Apo A, Apo B, Apo C, and Apo E.

3. (Original) The method of claim 2 wherein the apolipoprotein is selected from the group consisting of Apo A1 and Apo B.

4. (Previously Amended) The method of claim 1 wherein the antibodies are labeled with a detectable label.

5. (Previously Amended) The method of claim 1 further comprising determining the level of apolipoprotein in the saliva sample within less than three hours following collection.

6. (previously twice Amended) The method of claim 1 further comprising preparing the saliva in the sample by removing mucopolysaccharides from the saliva prior to determining the level of apolipoprotein in the saliva sample.

7. (previously amended) The method of claim 1 further comprising collecting the saliva after stimulating its secretion from a subject.

8. (original) The method of claim 1 further comprising determining the amount of albumin present in the saliva.

9. (previously twice Amended) The method of claim 8 further comprising correcting the determined amount of the apoplipoprotein for the presence of albumin in the saliva sample.

10. (previously twice amended) The method of claim 1 wherein the saliva sample is collected into a device which filters out mucopolysaccharides and which comprises the antibodies immunoreactive with one or more of the apolipoproteins in the saliva sample.

11. (original) The method of claim 10 wherein the apolipoprotein is either Apo A1 or Apo B.

12. (previously amended) An assay device or kit for determining the amount of apolipoprotein in a saliva sample comprising

means for collection of saliva,

antibodies immunoreactive with one or more apolipoproteins, wherein the antibodies are in a quantitative assay which measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith, and

standards of known amounts of apolipoproteins in saliva and serum.

13. (previously amended) The assay device or kit of claim 12 comprising filter means for removal of mucopolysaccharides from the saliva.

14. (previously amended) The assay device or kit of claim 12 wherein the antibodies are reactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, and Apo E.

15. (original) The assay device or kit of claim 12 further comprising antibodies immunoreactive with albumin.

16. (previously twice Amended) The assay device or kit of claim 12 wherein the antibodies immunoreactive with apolipoprotein in the saliva sample are immobilized on a solid support.

17. (original) The assay device or kit of claim 16 comprising reagents for detection of complexes between the apolipoprotein and the antibodies.

18. (previously Amended) The assay device or kit of claim 12 comprising a strip or dipstick.

19. (presently second time Amended) The assay device or kit of claim 15 comprising a first reagent consisting of antibodies to the apolipoprotein and a second reagent consisting of antibodies to albumin.

20. (previously Twice amended) A method for quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease from a saliva sample comprising

obtaining a saliva sample from an individual,

reacting the apolipoproteins in the saliva sample with antibodies immunoreactive with one or more of the apolipoproteins, wherein the antibodies are in a quantitative assay which measures the amount or concentration of bound complexes between apolipoproteins and the antibodies immunoreactive therewith,

determining the amount of apolipoproteins in the serum of the individual by comparing the immunoreactivity between the antibodies and apolipoproteins in the saliva sample by reference to standards of known amounts of apolipoproteins in saliva and serum from normal or at risk individuals.

21. (previously twice amended) The method of claim 1 further comprising,

correlating the levels of one or more lipoproteins selected from the group consisting of high density lipoprotein and low density lipoprotein, in the serum with the levels of apolipoprotein subtypes in the serum,

correlating the levels of the apolipoprotein subtypes in the serum based on the levels of apolipoprotein subtypes determined in the saliva sample, and

extrapolating the levels of the lipoprotein in the serum, based on the levels of the apolipoprotein subtypes determined in the saliva sample.

22. (previously amended) The method of claim 20 comprising reacting the apolipoprotein in the saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, and Apo E, and

correlating the levels of at least one apolipoprotein in the saliva with the levels of apolipoprotein in serum samples of patients having lipid disorders or risk of cardiovascular disease.

Claim 23 is cancelled.

TABLE OF CONTENTS

Certificate of Mailing

Appendix: Claims On Appeal

Table of Contents

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